

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
Washington, D.C.

in its capacity as elected Office

Date of mailing:

07 July 1994 (07.07.94)

International application No.:

PCT/US93/11060

Applicant's or agent's file reference:

B173 CIP PCT

International filing date:

15 November 1993 (15.11.93)

Priority date:

13 November 1992 (13.11.92)

Applicant:

PAPAYANNOPOULOU, Thalia

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

08 June 1994 (08.06.94)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

B. Schmitt

Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
DOCUMENT TRANSMITTED

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Washington D.C. 20231
United States of America

in its capacity as elected Office

Date of mailing:

13 February 1995 (13.02.95)

International application No.:

PCT/US93/11060

International filing date:

15 November 1993 (15.11.93)

Applicant:

BOARD OF REGENTS OF UNIVERSITY OF WASHINGTON et al

The International Bureau transmits herewith the following documents and number thereof:

copy of the international preliminary examination report and annexes (Article 36(3)(a))The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorised officer:

M. Abidine


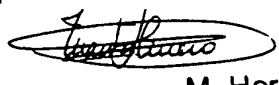
Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference B173CIP PCT(G 835)		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US 93/ 11060	International filing date (day/month/year) 15/11/1993	Priority date (day/month/year) 13/11/1992	
International Patent Classification (IPC) or national classification and IPC A61K39/395			
Applicant BOARD OF REGENTS OF UNIVERSITY OF WASHINGTON et al			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>5</u> sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consists of a total of <u>2</u> sheets.</p> <p>3. This report contains indications and corresponding pages relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand 08/06/1994		Date of completion of this report 01 FEB 1995	
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 cpmu d Fax: (+49-89) 2399-4465		Authorized officer  M. Herrero Telephone No.	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/US93/11060

I. Basis of the report

1. This report has been drawn up on the basis of:

☐ the international application as originally filed.

☒ the description, pages 1-4, 6-43 _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____,
pages 5, 5a _____, received on 19.12.94

☒ the claims, No. 1-28 _____, as originally filed,
No. _____, as amended under Article 19,
No. _____, filed with the demand,
No. _____, filed with the letter of _____,
No. _____, filed with the letter of _____,

☒ the drawings, sheets/fig 1/12-12/12 _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of: pages: 5 as originally filed _____
sheets of drawings/figures No.: _____.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed:

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/US93/11060

III. Non-establishment of opinion with regard to ~~novelty, inventive step and~~ industrial applicability

The questions whether the claimed invention appears ~~to be novel, to involve an inventive step (to be non-obvious), or~~ to be industrially applicable ~~have~~^{has} not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-28 _____

because:

☒ the said international application, or the said claims Nos. 1-28 _____ relate to the following subject matter which does not require an international preliminary examination (specify):

Methods for treatment of the human or animal body by surgery or therapy (PCT Rule 67.1 (iv)). For the assessment of the present Claims 1-28 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

☐ the description, claims or drawings (indicate particular elements below) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (specify):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Intern. application No.

PCT/US93/11060

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-28 _____	YES
	Claims _____	NO
Inventive Step (IS)	Claims 1-28 _____	YES
	Claims _____	NO
Industrial Applicability (IA)	Claims _____	YES
	Claims (1-28?, see Section III) _____	NO

2. CITATIONS AND EXPLANATIONS

The present application characterizes and claims a method suitable for the in vivo release of CD34⁺ cells from the bone marrow into the peripheral blood, which method relies on administering a blocking agent of VLA-4 antigen on the surface of the CD34⁺ cells.

Methods of treating cancer and AIDS, as well as a method for carrying out gene therapy based on the characterized procedure for peripheralizing CD34⁺ cells are also described and claimed.

The subject-matter of present Claims 1-28 is considered to meet the novelty and inventive step criteria set forth in Article 33(2) and (3) PCT in view of the fact that, in particular the release and mobilization of hematopoietic progenitor CD34⁺ cells, from their in vivo bone marrow microenvironment into the peripheral blood, brought about by the systemic administration of a blocking agent of VLA-4 antigen as hereby disclosed, appears to represent an effect neither anticipated nor suggested

by the available prior art documents, either if taken
alone or in any combination.

Integrins are a large family of integral membrane glycoproteins having over 16 heterodimeric members that mediate interactions between cells, interactions between cells and the extracellular matrix, and interactions involved in embryonic development and regulation of T-cell responses. Among integrins, the VLA-5 ($\alpha^5\beta_1$) complex is widely distributed and functions as a receptor for fibronectin. The VLA-4 ($\alpha^4\beta_1$) complex is expressed at substantial levels on normal peripheral blood B and T cells, thymocytes, monocytes, and some melanoma cells as well as on marrow blast cells and erythroblasts. Ligands for VLA-4 are vascular cell adhesion molecule-1 (VCAM-1) and CS-1, an alternately spliced domain within the Hep II region of fibronectin. Another group of integrins (CD11a/CD18, CD11b/CD18, and CD11c/CD18) share the common β_2 chain and are variably expressed on peripheral T cells, monocytes, and mature granulocytes. Ligands for β_2 -integrins include members of the Ig superfamily (ICAM-1 and ICAM-2) found on activated endothelial cells.

Issekutz, J. Immunol. 147:4178-4184 (1991), discloses that TA-2, a monoclonal antibody to rat VLA-4, inhibits the in vivo migration, of small peritoneal exudate lymphocytes and lymphocytes from peripheral lymph nodes, from the blood across the vascular endothelium to sites of inflammation. This document also observes that systemic treatment of rats with TA-2 was accompanied by an increase in total blood lymphocyte count.

Teixido et al., J. Clin. Invest. 90:358-367 (1992), teaches that in an in vitro model, interactions between VLA-4/VCAM-1, VLA-5/fibronectin and β_2 -integrin/ICAM-1 are all important for adhesion between bone marrow stromal cells and cells expressing

high levels of CD34. Simmons et al., Blood 80:388-395 (1992), teaches that in an in vitro model, adhesion between stromal cells and CD34⁺ cells was predominantly dependent on the VLA-4/VCAM-1 interaction and was
5 largely inhibited by monoclonal antibodies to either VLA-4 or VCAM-1, with fibronectin playing a minor role in binding. Williams et al., Nature 352:438-441 (1991), using in vivo mouse studies, teaches that adhesion of murine hematopoietic stem cells to stromal

- 5 -

Integrins are a large family of integral membrane glycoproteins having over 16 heterodimeric members that mediate interactions between cells, interactions between cells and the extracellular matrix, and interactions involved in embryonic development and regulation of T-cell responses. Among integrins, the VLA-5 ($\alpha^5\beta_1$) complex is widely distributed and functions as a receptor for fibronectin. The VLA-4 ($\alpha^4\beta_1$) complex is expressed at substantial levels on normal peripheral blood B and T cells, thymocytes, monocytes, and some melanoma cells as well as on marrow blast cells and erythroblasts. Ligands for VLA-4 are vascular cell adhesion molecule-1 (VCAM-1) and CS-1, an alternately spliced domain within the Hep II region of fibronectin. Another group of integrins (CD11a/CD18, CD11b/CD18, and CD11c/CD18) share the common β_2 chain and are variably expressed on peripheral T cells, monocytes, and mature granulocytes. Ligands for β_2 -integrins include members of the Ig superfamily (ICAM-1 and ICAM-2) found on activated endothelial cells.

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Replaced by ART 34



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 39/395, 37/02, 31/505 A61K 35/28, 48/00	A1	(11) International Publication Number: WO 94/11027 (43) International Publication Date: 26 May 1994 (26.05.94)
(21) International Application Number: PCT/US93/11060 (22) International Filing Date: 15 November 1993 (15.11.93) (30) Priority data: 07/977,702 13 November 1992 (13.11.92) US (60) Parent Application or Grant (63) Related by Continuation US 07/977,702 (CIP) Filed on 13 November 1992 (13.11.92) (71) Applicant (for all designated States except US): BOARD OF REGENTS OF UNIVERSITY OF WASHINGTON [US/US]; Office of Technology Transfer, 4225 Roosevelt Way, N.E., Suite #301, Seattle, WA 98105 (US).	(72) Inventor; and (75) Inventor/Applicant (for US only) : PAPAYANNOPOULOU, Thalia [US/US]; 3336 Cascadia Avenue South, Seattle, WA 98144 (US). (74) Agents: HALEY, James, F., Jr. et al.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 (US). (81) Designated States: AU, CA, JP, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: PERIPHERALIZATION OF HEMATOPOIETIC STEM CELLS (57) Abstract The invention provides methods for peripheralizing CD34 ⁺ cells, including hematopoietic stem cells. In a first aspect, the method comprises the step of administering a blocking agent of VLA-4 antigen on the surface of CD34 ⁺ cells. In a second aspect, the method comprises administering a blocking agent of VLA-4 antigen on the surface of CD34 ⁺ cells and administering a stimulating agent of CD34 ⁺ cell proliferation <i>in vivo</i> . The method according to the invention is useful in the treatment of cancer or AIDS, and in gene therapy.		

ional Application No

A. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

X Further documents are listed in the continuation of box C.

X Patent family members are listed in annex.

* Special categories of cited documents :

- T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- *X*** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y*** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z*** document member of the same patent family

Date of the actual completion of the international search

8 April 1994

Date of mailing of the international search report

715 -04- 1994

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Nooij, F

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF CLINICAL INVESTIGATIONS vol. 90, no. 2 , August 1990 , NEW YORK, USA pages 358 - 367 J. TEIXIDO ET AL. 'Role of beta 1 and beta 2 integrins in the adhesion of human CD34hi stem cells to bone marrow stroma.' cited in the application see the whole document ---	1-9,13, 14
P,X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA vol. 90, no. 20 , 15 October 1993 , WASHINGTON DC, USA pages 9374 - 9378 T. PAPAYANNOPOULOU ET AL. 'Peripheralization of hemopoietic progenitors in primates treated with anti-VLA4 integrin.' see the whole document ---	1-14
P,X	JOURNAL OF IMMUNOLOGY vol. 149, no. 11 , 1 December 1992 , BALTIMORE MD, USA pages 3759 - 3764 D. RYAN ET A. 'Inhibition of human bone marrow lymphoid progenitor colonies by antibodies to VLA integrins.' see abstract ---	1-3
P,X	BLOOD vol. 81, no. 1 , 1 January 1993 , NEW YORK, USA pages 112 - 121 J. LIESVELD ET AL. 'Expression of integrins and examination of their adhesive function in normal and leukemic hematopoietic cells.' see abstract -----	1-3

Information on patent family members

PCT/US 93/11060

Form PCT/ISA/210 (patent family annex) (July 1992)

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference B173 CIP PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 93/11060	International filing date (day/month/year) 15/11/93	(Earliest) Priority Date (day/month/year) 13/11/92
Applicant BOARD OF REGENTS OF UNIVERSITY et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 - ☒ filed with the international application.
 - ☐ furnished by the applicant separately from the international application,
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ Transcribed by this Authority
4. With regard to the title, ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
 - Figure No. ☐ as suggested by the applicant.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.
 - ☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 93/11060

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark : Although claims 1-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 93/11060

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 A61K39/395 A61K37/02 A61K31/505 A61K35/28 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BLOOD vol. 80, no. 2 , 15 July 1992 , NEW YORK, USA pages 388 - 395 P. SIMMONS ET AL. 'Vascular cell adhesion molecule-1 expressed by bone marrow stromal cells mediates the binding of hematopoietic progenitor cells.' cited in the application	1-9, 13, 14
Y	see abstract	25-28
Y	EP,A,0 455 482 (BECTON DICKINSON AND COMPANY) 6 November 1991 see claims	25-28
	--- -/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 April 1994

Date of mailing of the international search report

15 -04- 1994

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Nooij, F

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 93/11060

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF CLINICAL INVESTIGATIONS vol. 90, no. 2 , August 1990 , NEW YORK, USA pages 358 - 367 J. TEIXIDO ET AL. 'Role of beta 1 and beta 2 integrins in the adhesion of human CD34hi stem cells to bone marrow stroma.' cited in the application see the whole document ---	1-9, 13, 14
P,X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA vol. 90, no. 20 , 15 October 1993 , WASHINGTON DC, USA pages 9374 - 9378 T. PAPAYANNOPOULOU ET AL. 'Peripheralization of hemopoietic progenitors in primates treated with anti-VLA4 integrin.' see the whole document ---	1-14
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P,X	BLOOD vol. 81, no. 1 , 1 January 1993 , NEW YORK, USA pages 112 - 121 J. LIESVELD ET AL. 'Expression of integrins and examination of their adhesive function in normal and leukemic hematopoietic cells.' see abstract -----	1-3

INTERNATIONAL SEARCH REPORT

Information on patent family members

Information on patent family members

International Application No

PCT/US 93/11060

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0455482	06-11-91	AU-B- 641230	16-09-93
		AU-A- 7429391	07-11-91
		JP-A- 5076354	30-03-93
